

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015531 A2

(51) International Patent Classification⁷: **A23K**

(21) International Application Number: PCT/US02/24549

(22) International Filing Date: 1 August 2002 (01.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/310,513 6 August 2001 (06.08.2001) US

(71) Applicant and

(72) Inventor: GRUBER, Thomas [US/US]; 511 Westchester Drive, Rockford, IL 61107 (US).

(74) Agent: PICCIANO, Dante, J.; Bell, Boyd & Lloyd LLC, P.O. Box 1135, Chicago, IL 60690-1135 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,

DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL FORMULATION CONTAINING DYE

(57) Abstract: Methods and compositions for preventing abuse of dosage forms comprising an opioid analgesic and an aversive agent (e.g., a dye) in an effective amount to deter an abuser from administering a tampered form of the dosage form intravenously, intranasally, and/or orally are revealed.



WO 03/015531 A2

PHARMACEUTICAL FORMULATION CONTAINING DYE

The present application is related to U.S. Provisional Patent Application 60/310,513, filed August 6, 2001, the entire contents of which are hereby incorporated by reference and relied upon.

BACKGROUND OF THE INVENTION

Opioid analgesics are sometimes the subject of abuse. Typically, a particular dose of an opioid analgesic is more potent when administered parenterally as compared to the same dose administered orally. Therefore, one popular mode of abuse of oral opioid formulations involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any "suitable" vehicle for injection) in order to achieve a "high." Also, some formulations can be tampered with in order to provide the opioid agonist contained therein better available for illicit use. For example, a controlled release opioid agonist formulation can be crushed in order to provide the opioid contained therein available for immediate release upon oral or nasal administration. An opioid formulations can also be abusable by administration of more than the prescribed dose of the drug.

Opioid antagonists have been combined with certain opioid agonists in order to deter the parenteral abuse of opioid agonists. In the prior art, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as Talwin® Nx from Sanofi-Winthrop. Talwin®Nx contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of pain since 1978

(Valoron®N, Goedecke). A fixed combination of buprenorphine and naloxone was introduced in 1991 in New Zealand (Temgesic®Nx, Reckitt & Colman) for the treatment of pain. Purdue Pharma L.P currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40, 80 and 160 mg oxycodone hydrochloride under the tradename OxyContin.

U.S. Patent Nos. 5,266,331; 5,508,042; 5,549,912 and 5,656,295 disclose sustained release oxycodone formulations. U.S. Patent Nos. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

U.S. Patent No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms. PCT/US98/27257 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms. U.S. Patent No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

U.S. Patent No. 3,980,766 to Shaw et al., is related to drugs which are suitable for therapy in the treatment of narcotic drug addiction by oral use, e.g., methadone, formulated to prevent injection abuse through concentration of the active component in aqueous solution by incorporating in a solid dosage or tablet form of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

However, there still exists a need for a safe and effective treatment of pain with opioid analgesic dosage forms which are less subject to abuse than current therapies. All documents cited herein, including the foregoing, are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less parenteral abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less intranasal abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less oral abuse than other dosage forms.

It is a further object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less diversion than other dosage forms.

It is a further object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the abuse potential of the dosage form.

It is a further object of certain embodiments of the invention to provide a method of ~~manufacturing~~ an oral dosage form of an opioid analgesic such that it has less abuse potential.

These objects and others are achieved by the present invention, which is directed in part to an oral dosage form comprising an opioid analgesic; and at least one aversive agent for reducing the abuse of the opioid analgesic.

In certain embodiments of the present invention, the oral dosage forms of the present invention comprising an opioid analgesic; and an aversive agent or agents as a component(s) of

the dosage form helps to prevent injection, inhalation, and/or oral abuse by decreasing the "attractiveness" of the dosage form to a potential abuser.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a dye to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the dye is released when the dosage form is tampered with and provides a noticeable color or dye which makes the act of abuse visible to the abuser and to others such that the abuser is less likely to inhale, inject and/or swallow the tampered dosage form. For example, the dye can stain the mucous membrane of the nose and/or mouth and make the act of abuse noticeable to e.g., teachers, parents, peers, etc., whereby one may not want to abuse the drug due to the possible subsequent public scrutiny. Also, an abuser may be averted to injecting a solution containing extracted drug if the solution has a visible color.

In certain preferred embodiments, the dosage forms are controlled release oral dosage forms comprising a therapeutically effective amount of an opioid analgesic with the aversive agent described above such that the dosage form provides effective pain relief for at least about 12 hours, or at least about 24 hours when orally administered to a human patient.

In certain embodiments, may have a modified or sustained release as not to dump the aversive agent in a particular section of the gastrointestinal tract, e.g. the stomach, where it may cause an unwanted effect such as excessive irritation. The aversive agent can be combined with an enteric carrier to delay the release or combined with a carrier to provide a sustained release of the aversive agent. However, it is contemplated in the present invention that the aversive agent will not have any significant side effect (e.g., gastrointestinal side effect) even if all of the

aversive agent is immediately released upon oral administration of an intact dosage form as directed.

The term "aversive agent" is defined for purposes of the present invention to mean a dye, or combination of dyes.

The term "tampered dosage form" is defined for purposes of the present invention to mean that the dosage form has been manipulated by mechanical, thermal, and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating, (e.g., greater than about 45° C), or any combination thereof.

The phrase "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient.

The term "sustained release" is defined for purposes of the present invention as the release of the opioid analgesic from the oral dosage form at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range but below toxic levels over an extended period of time as compared to an immediate release product, e.g., from about 12 to about 24 hours. Preferably the sustained release is sufficient to provide a twice-a-day or a once-a-day formulation.

The term "particles" of aversive agent, as used herein, refers to granules, spheroids, beads or pellets comprising the aversive agent. In certain preferred embodiments, the aversive agent

particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

The term "parenterally" as used herein includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, infusion techniques, or other methods of injection known in the art.

The term "inhaled" as used herein includes trans-mucosal, trans-bronchial, and trans-nasal abuse.

The term "dye" as used herein includes a compound used to impart an indication of abuse to an abuser administering a tampered dosage form of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The aversive agents of the present invention are preferably for use in connection with oral dosage forms including opioid analgesics, which provide valuable analgesia but which may be abused. This is particularly true for controlled release opioid analgesic products which have a large dose of opioid analgesic intended to be released over a period of time in each dosage unit. Drug abusers typically may take a controlled-release product and crush, shear, grind, chew, dissolve and/or heat, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption by injection, inhalation, and/or oral consumption.

In certain embodiments, the present invention comprises the prevention or deterrence of the abuse of opioid analgesics by the inclusion of at least one aversive agent in the dosage form with the opioid analgesic.

In certain alternative embodiments, the present invention comprises the prevention or deterrence of the abuse of drugs other than opioid analgesics which may also be the subject of

abuse, by including at least one of the aversive agents described herein in a dosage form comprising the drug other than an opioid analgesic which is the subject of abuse.

Various dyes can be employed as the aversive agent, including for example, and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Green No. 1, FD&C Green No. 3, FD&C Green No. 5, FD&C Red No. 30, D&C Orange No. 5, D&C Red No. 8, D&C Red No. 33, caramel, and ferric oxide, red, other FD&C dyes and lakes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, combinations and mixtures thereof and other materials known to one of ordinary skill in the art. A full recitation of all FD&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, at Volume 5, Pages 857-884, which is incorporated herein by reference. The amount of dye used will vary as desired. Preferably the composition is non-toxic, edible, color stable in light and air and free of potential hazards to human health.

With the inclusion of a dye in the dosage form, when the dosage form is tampered with, the dye preferably imparts a color to the dosage form which makes the act of abuse visible to the abuser and others, such that the abuser is less likely to inhale, swallow, and/or inject the tampered dosage form. The dye may be added in an amount of from about 0.01 % to about 99%, preferably in an amount of from about 0.1 % to about 50% of the dosage form, most preferably in an amount of from about 0.1 % to about 10 % by weight of the dosage form. The percentage of the dye depends on the particular dye or dyes included in the dosage form, as the amount present should be in a sufficient amount to stain the mucous membrane and/or skin when the dosage form is abused nasally or orally. The dye may also stain the point of injection if a solution containing the dye is sufficiently colored. It is preferred that the dye (as well as the

other aversive agents) is at least partially dispersed in the opioid, rather than separate, e.g. in a film coat. This reduces the potential of the aversive agent from being separated from the opioid during the tampering process, making the aversive agent less or not effective. For safety reasons, the amount of the dye in the present invention should not be toxic to humans.

In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, the release of the aversive agent hinders, deters or prevents the administration of the tampered dosage form orally, intranasally, parenterally and/or sublingually.

The opioid agonists useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like. In certain embodiments, the amount of the opioid agonist in the claimed opioid composition may be about 75 ng to 750 mg.

In certain preferred embodiments, the opioid agonist is selected from the group consisting of hydrocodone, morphine, hydromorphone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol, or salts thereof or mixtures thereof. In certain preferred embodiments, the opioid agonist is oxycodone or hydrocodone.

In embodiments in which the opioid analgesic comprises hydrocodone, dosage forms may include analgesic doses from about 2 mg to about 50 mg of hydrocodone bitartrate. In embodiments in which the opioid analgesic comprises hydromorphone, the dosage form may include from about 2 mg to about 64 mg hydromorphone hydrochloride. In embodiments in which the opioid analgesic comprises morphine, the dosage form may include from about 2.5 mg to about 800 mg morphine sulfate, by weight. In embodiments in which the opioid analgesic comprises oxycodone, the dosage form may include from about 2.5 mg to about 320 mg oxycodone hydrochloride. The dosage form may contain more than one opioid analgesic to provide a therapeutic effect. Alternatively, the dosage form may contain molar equivalent amounts of other salts of the opioids useful in the present invention.

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple central nervous system and gastrointestinal actions. Chemically, hydrocodone is 4,5-epoxy-3-methoxy-17-methylnorphinan-6-one, and is also known as dihydrocodeinone. Like other opioids, hydrocodone may be habit forming and may produce drug dependence of the morphine type. In excess doses, hydrocodone, like other opium derivatives, will depress respiration.

Oral hydrocodone is also available in Europe (Belgium, Germany, Greece, Italy, Luxembourg, Norway and Switzerland) as an antitussive agent. A parenteral formulation is also available in Germany as an antitussive agent. For use as an analgesic, hydrocodone bitartrate is

commercially available in the United States only as a fixed combination with non-opiate drugs (i.e., ibuprofen, acetaminophen, aspirin, etc.) for relief of moderate or moderately severe pain.

A common dosage form of hydrocodone is in combination with acetaminophen, and is commercially available, e.g., as Lortab® in the U.S. from UCB Pharma, Inc. as 2.5/500 mg, 5/500 mg, 7.5/500 mg and 10/500 mg hydrocodone/acetaminophen tablets. Tablets are also available in the ratio of 7.5 mg hydrocodone bitartrate and 650 mg acetaminophen; and 7.5 mg hydrocodone bitartrate and 750 mg acetaminophen. Hydrocodone in combination with aspirin is given in an oral dosage form to adults generally in 1-2 tablets every 4-6 hours as needed to alleviate pain. The tablet form is 5 mg hydrocodone bitartrate and 224 mg aspirin with 32 mg caffeine; or 5 mg hydrocodone bitartrate and 500 mg aspirin. A relatively new formulation comprises hydrocodone bitartrate and ibuprofen. Vicoprofeno, commercially available in the U.S. from Knoll Laboratories, is a tablet containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen. The present invention is contemplated to encompass all such formulations, with the inclusion of one or more aversive agents as described herein.

Oxycodone, chemically known as 4,5-expoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, is an opioid agonist whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. The precise mechanism of its analgesic action is not known, but specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone is commercially available in the United States, e.g., as Oxycontin® from Purdue Pharma L.P. as controlled-release tablets for oral administration containing 10 mg, 20 mg, 40 mg or 80 mg oxycodone hydrochloride, and as OxyIR®, also from Purdue Pharma L.P.,

as immediate-release capsules containing 5 mg oxycodone hydrochloride. The present invention is contemplated to encompass all such formulations, with the inclusion of one or more aversive agents as described herein.

Additionally, agents other than opioid analgesics which are subject to abuse may be used in accordance with the present invention in place of the opioid analgesics in the dosage form.

Dosage Forms

The opioid analgesic formulation in combination with an aversive agent can be formulated as an immediate release formulation or controlled release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The controlled release dosage form may include a controlled release material which is incorporated into a matrix along with the opioid analgesic. In addition, the aversive agent may be separate from the matrix, or incorporated into the matrix.

The controlled release dosage form may optionally comprise particles containing or comprising the opioid analgesic, wherein the particles have diameters from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Additionally, the aversive agent may be incorporated into these particles, or may be incorporated into a tablet or capsule containing these particles. Preferably, the particles are film coated with a material that permits release of the opioid analgesic at a controlled rate in an environment of use. The film coat is chosen so as to achieve, in combination with the other stated properties, a desired in-vitro release rate. The controlled release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

In certain embodiments, the dosage forms of the present invention comprise normal release matrixes containing the opioid analgesic and the aversive agent.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads comprising an opioid analgesic, and a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. The one or more aversive agents may also be coated onto the beads comprising the opioid analgesic, may be prepared as separate beads and then combined in a dosage form including the controlled release beads comprising an opioid analgesic, or the aversive agent may be mixed in the dosage form with the controlled release beads comprising the opioid analgesic. In preferred embodiments where the opioid analgesic and the aversive agent are mixed in a capsule as different beads, the beads have an exact or similar appearance in order to deter an abuser from manually separating the beads prior to abuse in order to avoid the aversive substance. In tablet dosage forms, the aversive agent is preferably not included as a distinct layer which can be easier to separate from the active agent, although the present invention does encompass these embodiments.

The controlled release bead formulations of the present invention slowly release the
opioid analgesic, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the

method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with an opioid analgesic are prepared, e.g., by dissolving the opioid analgesic in water and then spraying the solution onto a substrate, for example, 18/20 beads, using a Wurster insert. Thereafter, the aversive agent is optionally added to the beads prior to coating. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the opioid to the beads. For example, a product which includes hydroxypropylmethylcellulose, etc. (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the opioid analgesic from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

Plasticized hydrophobic material may be applied onto the substrate comprising the opioid analgesic by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath,

fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said opioid analgesic when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the opioid analgesic, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the opioid analgesic from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The controlled release coatings of the present invention can also include erosion-promoting agents such as starch and gums. The controlled release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain. The release-modifying agent may also comprise a semi-permeable polymer. In certain preferred embodiments, the release-modifying agent is

selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The controlled release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864. The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

Matrix Formulations

In certain embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a controlled release coating as set forth herein. The present invention may also utilize a sustained release matrix that affords in-vitro dissolution rates of the opioid analgesic within desired ranges and releases the opioid analgesic in a pH-dependent or pH-independent manner.

A non-limiting list of suitable sustained-release materials which may be included in a sustained-release matrix according to the invention include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the opioid analgesic may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers, and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl

acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methylmethacrylate), poly(methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention.

The matrix also may include a binder. In such embodiments, the binder preferably contributes to the sustained-release of the opioid analgesic or pharmaceutically acceptable salt thereof from the sustained-release matrix. If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive. In certain preferred embodiments, a combination of two or more hydrophobic binder materials is included in the matrix formulations.

Preferred hydrophobic binder materials which may be used in accordance with the present invention include digestible, long chain (C_8 - C_{50} , especially C_{12} - C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 80% (by weight) of at least one digestible, long chain hydrocarbon.

In certain embodiments, the hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-,

di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to about 100°C.

In certain preferred embodiments, the dosage form comprises a sustained release matrix comprising an opioid analgesic, an aversive agent, and at least one water soluble hydroxyalkyl cellulose, at least one C₁₂-C₃₆, preferably C₁₄-C₂₂, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy (C₁ to C₆) alkyl cellulose, such as hydroxypropyl cellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose.

The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form may be determined, inter alia, by the precise rate of opioid analgesic release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol in the present oral dosage form may be determined, as above, by the precise rate of opioid analgesic release required. It may also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between about 20% and about 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between about 20% and about 50% (by wt) of the total dosage form.

In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the opioid analgesic from the formulation. In certain embodiments, a ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:1 and 1:4 is preferred, with a ratio of between 1:2 and 1:3 being particularly preferred.

In certain embodiments, the polyalkylene glycol may be, for example, polypropylene glycol, or polyethylene glycol which is preferred. The average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000, especially between 1,500 and 12,000.

Another suitable sustained-release matrix comprises an alkylcellulose (especially ethylcellulose), a C₁₂ to C₃₆ aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art.

In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention, there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating an opioid analgesic in a sustained-release matrix.

Incorporation in the matrix may be effected, for example, by:

(a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the opioid analgesic, and an aversive agent;

(b) mixing the at least one hydrophobic and/or hydrophilic material-containing granules with at least one C₁₂-C₃₆ aliphatic alcohol; and

(c) optionally, compressing and shaping the granules.

The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating the hydroxyalkyl cellulose, opioid analgesic, and an aversive agent with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid analgesic. Optionally, the opioid analgesic and/or the aversive agent is added extragranularly.

A sustained-release matrix can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material. Examples of sustained-release formulations prepared via melt-granulation techniques are found, e.g., in U.S. Patent No. 4,861,598.

The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial

release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid analgesic and at least one aversive agent, together with a sustained release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The matrix multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the opioid analgesic or pharmaceutically acceptable salt thereof for a time period of at least about 12 hours.

An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic sustained release material, the opioid analgesic, the aversive agent, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into matrix multiparticulates having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

Optionally, the aversive agent may be added to a dosage form including multiparticulates comprising opioid analgesic (without the aversive agent).

Plasticizers, such as those described above, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix.

Other pharmaceutical excipients, e.g., talc, mono- or polysaccharides, lubricants and the like may be included in the sustained release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

A melt extruded matrix multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded matrix multiparticulate(s)" and "melt-extruded matrix multiparticulate system(s)" and "melt-extruded matrix particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic sustained release material as described herein. Preferably the melt-extruded matrix multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded matrix multiparticulates can be any geometrical shape within this size range. In certain embodiments, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded matrix multiparticulates within a capsule. For example, a plurality of the melt-extruded matrix multiparticulates may be placed in a gelatin capsule in an amount

sufficient to provide an effective sustained release dose when ingested and contacted by gastrointestinal fluid.

In another embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques.

Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980). In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Patent No. 4,957,681 (Klimesch et. al.).

Optionally, the sustained-release matrix multiparticulate systems, tablets, or capsules can be coated with a sustained release coating such as the sustained release coatings described herein. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic sustained-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the desired release rate. The coating can optionally contain the aversive agent. In such embodiments, an optional second overcoat can be applied as to minimize the perception of the aversive agent when a dosage form of the present invention is administered intact.

The dosage forms of the present invention may further include combinations of melt-extruded matrix multiparticulates containing an opioid analgesic; an aversive agent; or mixtures thereof. Furthermore, the dosage forms can also include an amount of an immediate release opioid analgesic for prompt therapeutic effect. The immediate release opioid analgesic may be incorporated, e.g., as separate multiparticulates within a gelatin capsule, or may be coated on the surface of, e.g., melt extruded matrix multiparticulates.

The sustained-release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of sustained-release material, by varying the amount of plasticizer relative to other matrix constituents, by varying the amount of hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, melt-extruded formulations are prepared without the inclusion of the opioid analgesic; the aversive agent; or mixtures thereof; which is added thereafter to the extrudate. Such formulations typically will have the opioid analgesic; the aversive agent; or mixtures thereof blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the opioid analgesic; the aversive agent; or mixtures thereof included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

Typical melt-extrusion production systems suitable for use in accordance with the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and a meter. In addition, the production system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the production system will include an extruder such as a twin-screw extruder which consists of two counter-rotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof. The feed materials enter through a feed hopper and are moved through the barrel by the screws and are forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to

render the extruded ropes into the matrix multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, New Jersey. Other suitable apparatus will be apparent to those of ordinary skill in the art.

A further aspect of the invention is related to the preparation of melt-extruded matrix multiparticulates as set forth above in a manner which controls the amount of air included in the extruded product. By controlling the amount of air included in the extrudate, the release rate of the opioid analgesic; the aversive agent; or mixtures thereof may be altered.

Thus, in a further aspect, of the invention, the melt-extruded product is prepared in a manner which substantially excludes air during the extrusion phase of the process. This may be accomplished, for example, by using a Leistritz extruder having a vacuum attachment. The extruded matrix multiparticulates prepared according to the invention using the Leistritz extruder under vacuum provides a melt-extruded product having different physical characteristics. In particular, the extrudate is substantially non-porous when magnified, e.g., using a scanning electron microscope which provides an SEM (scanning electron micrograph). Such substantially non-porous formulations may provide a faster release of the therapeutically active agent, relative to the same formulation prepared without vacuum. SEMs of the matrix multiparticulates prepared using an extruder under vacuum appear very smooth, and the multiparticulates tend to be more robust than those multiparticulates prepared without vacuum. It has been observed that in at least certain formulations, the use of extrusion under vacuum provides an extruded matrix multiparticulate product which is more pH-dependent than its counterpart formulation prepared without vacuum. Alternatively, the melt-extruded product is prepared using a Werner-Pfleiderer twin screw extruder.

In certain embodiments, a spheronizing agent is added to a granulate or matrix multiparticulate and then spheronized to produce sustained release spheroids. The spheroids are then optionally overcoated with a sustained release coating by methods such as those described above.

Spheronizing agents which may be used to prepare the matrix multiparticulate formulations of the present invention include any art-known spheronizing agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (TradeMark, FMC Corporation). The spheronizing agent is preferably included as about 1 to about 99% of the matrix multiparticulate by weight.

In certain embodiments, in addition to the opioid analgesic, the aversive agent, and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively), the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

In certain embodiments, a sustained release coating is applied to the sustained release spheroids, granules, or matrix multiparticulates. In such embodiments, the sustained-release coating may include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein. The coating is preferably derived from an aqueous dispersion of the hydrophobic sustained release material.

In certain embodiments, it is necessary to overcoat the sustained release spheroids, granules, or matrix multiparticulates comprising the opioid analgesic, the aversive agent, and sustained release carrier with a sufficient amount of the aqueous dispersion of, e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25%, in order to obtain a sustained-release formulation. The overcoat may be lesser or greater depending upon, e.g., the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same. Cellulosic materials and polymers, including alkylcelluloses, are sustained release materials well suited for coating the sustained release spheroids, granules, or matrix multiparticulates according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating

plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly to the sustained release spheroids, granules, or matrix multiparticulates.

In other preferred embodiments of the present invention, the sustained release material comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in the National Formulary (NF) XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there is a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates,

commercially available as Eudragit® from Röhm GMBH and Co., Kg Darmstadt, Germany. There are several different types of Eudragit®. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about $\text{pH} < 5.7$ and is soluble at about $\text{pH} > 6$. Eudragit S does not swell at about $\text{pH} < 6.5$ and is soluble at about $\text{pH} > 7$. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent; however, dosage forms coated with Eudragit RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Röhm under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained-release formulation having a desirable dissolution profile. Desirable sustained-release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L. In

embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic sustained release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained-release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained-release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

In certain embodiments, the uncoated/coated sustained release spheroids, granules, or matrix multiparticulates containing the opioid analgesic; and the aversive agent; are cured until an endpoint is reached at which the sustained release spheroids, granules, or matrix multiparticulates provide a stable dissolution of the opioid. The curing endpoint may be determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40°C and a relative humidity of 75%. Cured formulations are described in detail in U.S. Patent Nos. 5,273,760; 5,286,493; 5,500,227; 5,580,578; 5,639,476; 5,681,585; and 6,024,982. Other examples of sustained-release formulations and coatings which may be used in accordance with the present invention include U.S. Patent Nos. 5,324,351; 5,356,467; and 5,472,712.

In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical

Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

It has further been found that the addition of a small amount of talc to the sustained release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

Osmotic Dosage Forms

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the opioid analgesic and optionally the aversive agent) and a delivery or push layer (which may contain the aversive agent), wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which the opioid analgesic can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the sustained metered release of opioid analgesic from the dosage form. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide

a releasing-pore of a sustained-release rate are disclosed in U.S. Patent Nos. 4,200,098 and 4,285,987.

In certain embodiments, the bilayer core comprises a drug layer with opioid analgesic and a displacement or push layer optionally containing the aversive agent. The aversive agent may optionally be included in the drug layer instead of or in addition to being included in the push layer. In certain embodiments, the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_n \cdot H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average

molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the contents of the drug layer from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates.

Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented

by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropyl isopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphanatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a substantially homogenous core comprising opioid analgesic, an aversive agent, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The substantially homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the opioid analgesic, and the aversive agent.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkynylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethylcellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Patent Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Patent No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} ($\text{cm}^2/\text{hr-atm}$) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the art in U.S. Patent Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate, and vinyl stearate.

Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

The oral dosage form and methods for use of the present invention may further include, in addition to an opioid analgesic and an aversive agent, one or more drugs that may or may not act synergistically with the opioid analgesic. Thus, in certain embodiments, a combination of two opioid analgesics may be included in the dosage form. For example, the dosage form may include two opioid analgesics having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing.

In yet further embodiments, one or more opioid analgesic is included and a further non-opioid drug is also included. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin, acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cyclooxygenase-II inhibitors (COX-II or COX-2 inhibitors); and/or glycine receptor antagonists.

In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the opioid analgesic by virtue of the inclusion of an additional non-opioid analgesic, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans are reduced.

Suitable non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxipinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflunisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Useful dosages of these drugs are well known to those skilled in the art.

N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that block a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM₁, or GT_{1b}, a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Pat. Nos. 5,321,012 and 5,556,838 (both to Mayer et al.), and to treat chronic pain in U.S. Pat. No. 5,502,058 (Mayer et al.), all of which are hereby incorporated by reference. The NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer et.al. patents.

The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Pat. No. 5,514,680 (Weber et al.).

COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S.

Patent Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain preferred COX-2 inhibitors include celecoxib (SC58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), MK-966 (also known as Vioxx), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof. Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per day are therapeutically effective in combination with an opioid analgesic. Alternatively, about 0.25 mg to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with an opioid analgesic.

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed opioid analgesics. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparinate, glutamate and the like.

Some of the opioid analgesics disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

The oral dosage forms of the present invention may be in the form of tablets, troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, etc.

In certain embodiments, the present invention provides for a method of preventing abuse of an oral controlled release dosage form of an opioid analgesic comprising preparing the dosage forms as described above.

In certain embodiments, the present invention provides for a method of preventing diversion of an oral controlled release dosage form of an opioid analgesic comprising preparing the dosage forms as described above.

In certain embodiments, the present invention provides for a method of treating pain by administering to a human patient the dosage forms described above.

The following example illustrates various aspects of the present invention. It is not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1**A 20 mg oxycodone formulation containing a dye is prepared**

FD & C Blue #2 dye is a water-soluble compound. An amount of this compound suitable for use in the present invention is added to an oxycodone formulation during the granulation process. Other coloring agents as described herein could also be used. The oxycodone formulation of Example 1 is listed in Table 1 below.

TABLE 1

Ingredients	Amt/Unit mg	Amount/Batch gm
Ox codone HCl	20.0	209.6*
Spray Dried Lactose	59.25	592.5
Povidone	5.0	50.0
Eudragit RS30D (solids)	10.0	100
Triacetin	2.0	20.0
FD & C Blue #2	1.2	6.12
Stearyl Alcohol	25.0	250.0
Talc	2.5	25.0
Magnesium Stearate	1.25	12.5
Opadry Pink Y-S-14518A	5.0	50.0
Total	136.8	1377.7

*adjusted for 99.6% assay and 4.2% residual moisture.

*adjusted for 99.23% assay and 0.5% residual moisture.

Process:

1. Dispersion: Disperse Eudragit and Triacetin in an aqueous solution to form Eudragit/Tracetin dispersion.
2. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.
3. Milling: Discharge the granulation and pass through a mill.
4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.
5. Milling: Pass the cooled granulation through a mill.
6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
7. Compression: Compress the granulation into tablets using a tablet press.

All patents, articles and references cited herein are hereby incorporated by reference in their entirety and relied upon.

CLAIMS

What is claimed is:

1. An oral dosage form comprising:
a therapeutically effective amount of an opioid analgesic; and
a dye in an effective amount to impart an indication of abuse to an abuser upon administration of said dosage form after tampering.
2. The oral dosage form of claim 1, wherein the dye is selected from the group consisting of an FD&C dye, an FD&C lake, caramel, ferric oxide, natural coloring agents, and mixtures thereof.
3. The oral dosage form of claim 1, wherein the dye is an FD&C dye selected from the group consisting of FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Green No. 1, FD&C Green No. 3, FD&C Green No. 5, FD&C Red No. 30, D&C Orange No. 5, D&C Red No. 8, D&C Red No. 33, and mixtures thereof.
4. The oral dosage form of claim 1, wherein the dye is a natural coloring agent selected from the group consisting of grape skin extract, beet red powder, betacarotene, annato, carmine, turmeric, paprika, and mixtures thereof.
5. The oral dosage form of claim 1, wherein the dye is FD&C Blue No. 2.
6. The oral dosage form of claim 1, wherein the dye is in an amount of about 0.01% to about 99 % by weight of the dosage form.
7. The oral dosage form of claim 1, wherein the dye is in an amount of about 0.1% to about 50% by weight of the dosage form.

8. The oral dosage form of claim 1, wherein the dye is in an amount of about 0.1% to about 10 % by weight of the dosage form.
9. The oral dosage form of claim 1, wherein said opioid analgesic is morphine or a pharmaceutically acceptable salt thereof.
10. The oral dosage form of claim 1, wherein said opioid analgesic is hydromorphone or a pharmaceutically acceptable salt thereof.
11. The oral dosage form of claim 1, wherein said opioid analgesic is hydrocodone or a pharmaceutically acceptable salt thereof.
12. The oral dosage form of claim 1, wherein said opioid analgesic is oxycodone or a pharmaceutically acceptable salt thereof.
13. The oral dosage form of claim 1, wherein said opioid analgesic is codeine or a pharmaceutically acceptable salt thereof.
14. The oral dosage form of claim 1, wherein said opioid analgesic is tramadol or a pharmaceutically acceptable salt thereof.
15. The oral dosage form of claim 1, wherein said administration is parenteral administration.
16. The oral dosage form of claim 1, wherein said administration is nasal administration.
- 17. ~~The oral dosage form of claim 1, wherein said administration is oral administration.~~
18. The oral dosage form of claim 1, further comprising a pharmaceutically acceptable excipient.
19. The oral dosage form of claim 18, wherein said excipient is a sustained release excipient.

20. The oral dosage form of claim 19, wherein said dosage form provides an analgesic effect for at least about 12 hours after oral administration to a human patient.
21. The oral dosage form of claims 1-20 wherein said dye is at least partially interdispersed with the opioid analgesic.
22. A method of treating pain comprising administering to a patient an oral dosage form of claims 1-21.
23. A method of preparing a pharmaceutical dosage form comprising combining a therapeutically effective amount of an opioid analgesic in a dosage form with an effective amount of a dye to impart an indication of abuse to an abuser administering said dosage form after tampering.
24. The method of claim 23, wherein said dye is at least partially interdispersed with the opioid analgesic.
25. A method of preventing abuse of an oral dosage form of an opioid analgesic comprising:
preparing the dosage form with an analgesically effective amount of an opioid analgesic;
and
a dye in an effective amount to impart an indication of abuse to an abuser
administering a tampered dosage form of the present invention.
26. An oral dosage form comprising:
a therapeutically effective amount of an opioid analgesic; and
a dye in an effective amount to deter an abuser from administering said dosage form after tampering.